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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/389,565	09/03/1999	DAVID M. NEVILLE, JR.	14028.0290	5574

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	22

DATE MAILED: 01/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/389,565	Applicant(s) Neville et al.
	Examiner G. R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 21, 2001*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on 11/21/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/389,565 is acceptable and a CPA has been established. An action on the CPA follows.

2. In view of the papers filed 11/21/01, the inventorship in this nonprovisional application has been changed by the deletion of Joshua E. Scharff.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 21-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al (V on form PTO-892) in view of Neville et al (AJ on form PTO-1449 filed December 6, 1999), Hirsch et al (AS on form PTO-1449 filed December 6, 1999) and Whitlow et al (74A on form PTO-1449 filed December 6, 1999), all of record.

It was stated previously: "The Chaudhary et al reference teaches the construction of single chain anti-Tac (anti-Tac(Fv)) antibodies which are linked to a truncated form of diphtheria toxin (DT388) consisting of the first 388 amino acids of the toxin. Chaudhary et al teaches that this DT388-anti-Tac(Fv) construct is effective in eliminating cells bearing the p55 subunit of the IL-2R. Chaudhary et al teaches that the DT388 truncated form of diphtheria toxin lacks the diphtheria receptor binding site (page 9491 in particular) and therefore cannot indiscriminately bind to and kill cells which do not bear the determinant recognized by the scFv. While Applicant's more specific claims (26 and 31-37) are drawn to a DT390 species consisting of the first 390 amino acids of the toxin, the effect is the same, i.e., the removal of the diphtheria receptor binding site, and the two additional amino acids of DT390 do not appear to confer any special properties beyond the properties of the DT388 polypeptide taught by Chaudhary et al. Therefore, the instantly disclosed and claimed DT390 appears to be obvious over the DT388 of Chaudhary et al, absent a showing of unobvious properties. Chaudhary et al does not teach an anti-CD3 antibody. Neville et al teaches the use of an immunotoxin conjugate comprising diphtheria toxin and the anti-CD3 antibody UCHT1 for the in vivo treatment of a T cell leukemia in a murine model. It is well known in the art that CD3 is exclusive to and pan-activated T cell, while IL-2R (the anti-Tac target) is not as ubiquitous on activated T cells and is more widely expressed on immune cells, including B cells. Neville et al also teaches that an anti-CD3 antibody-diphtheria toxin conjugate would be effective in the treatment of both graft-versus-host disease (page 2588, paragraph bridging columns in particular), autoimmune disease (page 2588, second column in particular) and AIDS, the latter because anti-CD3 can recognize and kill resting T cells, thereby helping to eliminate latent HIV particles (page 2588, second column in particular). Neville et al teaches whole antibody, not scFv. However, Hirsch et al teaches that anti-CD3 $F(ab')_2$ fragments (lacking the Fc portion of the molecule) are immunosuppressive without the complications sometimes associated with the use of whole molecules anti-CD3 antibodies (Abstract in particular). Hirsch et al further teaches that treatment with anti-CD3 $F(ab')_2$ fragments is effective in the inhibition of the rejection of skin grafts. Whitlow et al teaches that incorporation of antibody variable domains into a single scFv gene simplifies antibody engineering and that engineering an scFv molecule into a fusion protein combines the antigen specificity of the parent antibody with the effector function of the fusion partner (page 97 in particular). Whitlow et al further teaches

the GGGGSGGGGSGGGS linker polypeptide (Table 2 in particular) and that linker design and usage is not particularly problematic (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to replace the scFv anti-Tac member of the truncated diphtheria toxin taught by Chaudhary et al with the anti-CD3 member of the immunotoxin taught by Neville et al as an scFv due to the fact that CD3 is a truer marker of T cells and that Hirsch et al teaches that antigen binding fragments of anti-CD3 are preferable over whole molecule and the teachings of Whitlow et al that scFvs simplify production of the antibody-toxin. One would have been motivated with a reasonable expectation of success to combine the teachings based upon the fact that one would want to more specifically target the cells responsible for the etiology of a subject's condition and the fact that single purification of a fusion protein is faster and more efficient that purification and conjugation of multiple cell products."

6. Claims 21-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al (V on form PTO-892) in view of Neville et al (AJ on form PTO-1449 filed December 6, 1999), Hirsch et al (AS on form PTO-1449 filed December 6, 1999), Whitlow et al (74A on form PTO-1449 filed December 6, 1999) and Youle et al (V on form PTO-892), all of record.

It was stated previously: "The Chaudhary et al, Neville et al, Hirsch et al and Whitlow et al references have been discussed supra. The Youle et al reference is additive to the teachings of Neville et al regarding the use of UCHT1-diphtheria toxin conjugates for the treatment of graft-versus-host disease (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use anti-CD3 conjugated with truncated diphtheria toxin for the reasons above and would be further motivated with a reasonable expectation of success by the teaching of Youle et al anti-CD3-diphtheria toxin was more effective and efficient at killing T cells than other antibody/toxin combinations."

7. No claim is allowed.

8. All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next

Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Friday from 8:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
January 16, 2002

Patrick J. Nolan, Ph.D.
Primary Examiner
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